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INSIDE

More on Lymphoma Treatment in the Elderly: Results from Korea

ABSTRACT & COMMENTARY

Synopsis: *In a series from Korea, treatment outcomes for older (age older than 60 years) patients with diffuse large-cell lymphoma were analyzed with particular focus on dose intensity of doxorubicin. Although, overall, older patients did not achieve the same level of complete response, for those who were able to maintain doxorubicin dose intensity, response rates were comparable to younger patients.*

Source: Lee KW, et al. *Cancer*. 2003;98:2651-2656.

Lymphoma occurs more commonly in older patients, and there remains some controversy about response rates and survival for patients in this age group. In recent years there has been an emphasis on chemotherapy dose intensity, and it has been speculated that the difference in treatment responses is due to the delivered dose and not an a priore increased resistance of lymphoma in older patients to treatment. In examining this question, Lee and colleagues from Seoul National University Hospital in the Republic of Korea retrospectively examined the course of 195 patients with diffuse large-cell lymphoma treated at their institution. Of these, 70 were considered "elderly" (aged 60 years or older). All patients were treated with doxorubicin-based chemotherapy (CHOP—cyclophosphamide, doxorubicin, vincristine, and prednisone; or COPBLAM-V—cyclophosphamide, vincristine, bleomycin, doxorubicin, procarbazine and prednisone).

Overall, elderly patients had poorer treatment outcomes than did young patients (5-year survival, 30% vs 57%; $P < .001$). However, elderly patients who received doxorubicin at dose intensities of > 10 mg/m^2 per week (n = 25) had outcomes (5-year survival, 52%) that were comparable to those of young patients. Among prognostic factors, only International Prognostic Index score ($P = .022$) and dose intensity of doxorubicin ($P = .039$) were found to have significant effects on the overall survival of elderly patients. When the reasons for doxorubicin dose reduction in 45 elderly patients who ultimately received doxorubicin dose reductions to less than 10 mg/m^2/wk were analyzed, it was found that 20 patients received reduced doses from the start of treatment because of their old age alone.

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COMMENT BY WILLIAM B. ERSHLER, MD

This analysis highlights an important concept in the explanation for the observed reduced response rates and survival for elderly patients treated for lymphoma. When treated equally, older patients fare as well as younger in parameters such as response rate and survival. However, there is, without question, increased susceptibility to certain adverse consequences of therapy, most notably marrow cytopenias. Accordingly, there remains reluctance among some providers to use full-dose chemotherapy (or even chemotherapy at all) for fear of the risks of neutropenia. In the era of aggressive supportive management, such reluctance may be overcome. Primary, prophylactic marrow stimulatory factor support has become common practice in the treatment of at-risk populations, including the elderly, and current ASCO, EORTC and NCCN guidelines support such an approach.[1] Yet, it is noteworthy that a recent European report did not demonstrate improved outcomes in elderly patients treated with up-front G-CSF. Thus, although it seems a logical approach, further investigation is required before older lymphoma patients should routinely be treated with growth factors coincident with their first exposure to chemotherapy.

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Oral Capecitabine as an Alternative to IV 5-fluorouracil-Based Adjuvant Therapy for Colon Cancer: Safety Results of a Randomized, Phase III Trial

ABSTRACT & COMMENTARY

Synopsis: *Based on its improved safety profile, capecitabine has the potential to replace 5-FU/LV as standard adjuvant treatment for patients with colon cancer.*

Source: Scheithauer, et al. *Ann Oncol*. 2003;14:1735-1743.

Numerous clinical trials have demonstrated that adjuvant treatment with fluoropyrimidines improves outcomes for patients with resected colon cancer. There have been pooled analyses confirming increases in event-free and overall survival from therapy with 5-fluorouracil plus leucovorin.[1]

It is currently accepted that treatment with 5-FU/LV for 6-8 months is the standard adjuvant therapy for Dukes' C (stage III) colon cancer, with trials showing no difference in the efficacy of weekly and monthly 5-FU/LV regimens.[2] The efficacy of adjuvant therapy for high-risk Dukes' B has also been demonstrated.[3] Adjuvant treatment has also been shown to benefit older patients despite their low participation in clinical trials.[4,5] There is also evidence that there is a considerable discrepancy between consensus recommendations and the use of adjuvant treatment in the community, particularly for older patients.[6,7]

In a randomized trial, treatment was discontinued in 24% of patients, primarily due to toxicity and lack of compliance.[8] Capecitabine is an oral fluoropyrimidine that generates 5-FU preferentially in tumor tissue via a 3-step enzymatic sequence. Oral capecitabine is effective in the treatment of metastatic colorectal cancer.[9,10]

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EDITORIAL GROUP HEAD: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
ASSISTANT MANAGING EDITOR: Robert Kimball.
SENIOR COPY EDITOR: Christie Messina Petrone.

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Robert Kimball, Assistant Managing Editor, at (404) 262-5413 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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Capecitabine achieves a superior response rate and at least equivalent time to disease progression and overall survival compared with 5-FU/LV and an improved safety profile.[11] The majority of patients prefer oral- and home-based therapy as long as efficacy is not compromised. The current international, multicenter, randomized, open-label phase III study evaluated capecitabine vs IV 5-FU/LV (Mayo Clinic regimen) as adjuvant therapy for patients with Dukes' C colon cancer. This paper reports the planned safety analysis of 1987 patients.

COMMENT BY STUART M. LICHTMAN, MD

The study eligibility included patients aged 18-75 years who had histologically confirmed Dukes' C colon carcinoma after surgery with curative intent. Patients were randomized to receive 24 weeks of treatment with either oral capecitabine 1250 mg/m^2 twice daily, given on days 1-14 every 21 days or IV leucovorin 20 mg/m^2 followed by IV bolus 5-FU 425 mg/m^2, days 1-5 every 28 days. In all, 1987 patients were enrolled in 164 centers. Patients receiving capecitabine experienced significantly less diarrhea (46% vs 64%), nausea/vomiting (36% vs 51%), stomatitis (22% vs 60%), alopecia (6% vs 22%), and neutropenia (2% vs 8%). Only hand-foot syndrome was more common with capecitabine (62% vs 10%). Grade 3 hyperbilirubinemia was more common with capecitabine (18.6% vs 5.9%). Capecitabine showed a more favorable safety profile than 5-FU/LV in both younger and older patients. Older patients had more severe toxicity with the 5-FU/LV regimen; in capecitabine-treated patients there was no age difference. Premature withdrawal due to adverse events occurred in 12% of patients receiving capecitabine and 8% of those receiving 5-FU/LV. Overall, there was a low incidence of all-cause, 60-day mortality, with 5 deaths in the capecitabine arm and 4 in the 5-FU/LV arm.

The current study is the first step to try to determine whether an oral regimen can replace IV therapy for the adjuvant treatment of colon cancer. A less-toxic regimen would hopefully lead to greater compliance and allow more patients to benefit from therapy. This study showed that capecitabine might fulfill some of these criteria when compared to the Mayo Clinic adjuvant regimen. This regimen may have been a too-toxic comparator for single-agent capecitabine. There are alternative 5-FU/LV regimens that have less toxicity, particularly in older patients, which may have also been appropriate.[12,13] There are emerging results from oxaliplatin combined with bolus/infusion 5-FU/LV as adjuvant treatment.[14] Capecitabine may be an attractive alternative to replace 5-FU/LV in this regimen. A large, international study has shown that capecitabine in combination with oxaliplatin is active, first-line treatment for metastatic colorectal cancer, achieving similar efficacy.[15] The conclusion is that from a safety perspective, capecitabine can replace 5-FU/LV as the standard adjuvant treatment for patients with colon cancer. ■

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The Significance of Imatinib Mesylate (Gleevec®)-Induced Cytopenias in Patients with Chronic-Phase CML

ABSTRACT & COMMENTARY

Synopsis: *In a series of chronic-phase CML patients who had previously been treated with interferon and who subsequently received imatinib mesylate, the appearance of myelosuppression (Grade > 3 neutropenia or thrombocytopenia) was associated with significantly less frequent major or complete cytogenetic responses.*

Source: Sneed TB, et al. *Cancer*. 2004;100:116-121.

Imatinib mesylate (Gleevec®) is a potent and selective tyrosine kinase inhibitor against Bcr/Abl, the protein product of the Philadelphia chromosome.[1]

The drug, administered orally, has rapidly become first-line therapy for patients with chronic myelogenous leukemia (CML). One major advantage of Gleevec, in addition to its remarkable effectiveness, is that it is relatively nontoxic. Non-myeloid toxicities are usually mild and infrequently require dose reductions or delays. However, myelotoxicity occurs more commonly. In the current series, 45% of chronic-phase CML patients who were treated with imatinib at 400 mg/d after they had failed treatment with interferon developed grade ≥ 3 myelosuppression requiring either dose modification or delay. The prognostic importance of the myelosuppression is the subject of this report.

Sneed and colleagues analyzed 143 consecutive patients seen at M.D. Anderson Cancer Center in 1999 and 2000. These patients had all received prior interferon α and were part of a multi-institutional study examining the efficacy of imatinib in this population. During the therapy, neutropenia ≥ Grade 3 (according to National Cancer Institute Common Toxicity Criteria) occurred in 64 patients (45%), and thrombocytopenia > Grade 3 occurred in 31 patients (22%). Any myelosuppression ≥ Grade 3 was associated with a lower rate of major (P = .04) or complete (P = .01) cytogenetic responses. This was more pronounced with myelosuppression that lasted more than 2 weeks. The major cytogenetic response rate was 58% with Grade ≥ 3 myelosuppression compared with a rate of 75% without Grade ≥ 3 myelosuppression (P = .03); the complete cytogenetic response rates were 36% and 63%, respectively (P = .001).

In multivariate analysis, pretreatment platelet count, imatinib dose reductions, and duration of imatinib-induced myelosuppression were associated significantly with response.

COMMENT BY WILLIAM B. ERSHLER, MD

One logical explanation for the less favorable outcomes observed in those who experienced myelosuppression is the corresponding reduced dose of imatinib delivered. As is the case with other hematologic and non-hematologic tumors, delivery of the planned dose on time is an apparent favorable prognostic factor.[2,3] Yet, it is conceivable that myelosuppression in response to imatinib is a selective feature of a marrow that has more extensive disease or is indicative of a biological feature of more advanced disease. Under any circumstance, the finding is of importance because it is now apparent that those chronic-phase patients who experience myelosuppression with conventional dose imatinib have a reduced rate of achieving optimal response (complete cytogenetic remission). Use of colony-stimulating factor in an effort to maximize exposure to imatinib is one potential solution, but this approach will require careful clinical investigation before it should be adopted as a standard of care.

It is notable that the relatively high rate of myelosuppression observed in this series of previously treated (with interferon) patients may exceed what is currently observed, as imatinib has moved up to first-line therapy in many practices. It will be interesting to examine current series for the prevalence of myelosuppression in those exposed to imatinib as first-line treatment. ■

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Temozolomide (Temodur®) Treatment and Immunodeficiency in Melanoma Patients

ABSTRACT & COMMENTARY

Synopsis: *Temozolomide has been used for the treatment of melanoma with effects comparable to DTIC, and regimens are currently under development that involve more extensive administration. In this report from Memorial Sloan Kettering, patients treated on a daily schedule for 6 weeks or more before a treatment break were observed to develop significant lymphopenia and a higher-than-expected incidence of opportunistic infections.*

Source: Su YB, et al. *J Clin Oncol*. 2004;22:610-616.

Temozolomide (TMZ) is an oral chemotherapeutic agent that is metabolized to the alkylating agent 5-(3-methyltriazen-1-yl)imidazole-4-carboximimide, which is the active metabolite of dacarbazine (DTIC). Like DTIC, TMZ has shown some activity against melanoma,[1] but, unlike DTIC, it is 100% bioavailable after oral dosing. The schedule most commonly used for TMZ in the treatment of melanoma is 150-200 mg/m^2 orally, daily for 5 days every 4 weeks. Su and colleagues at Memorial Sloan Kettering Cancer Center used a more intensive dosing schedule of TMZ in an effort to improve response rates. TMZ was administered to 97 patients at 75 mg/m^2/d orally for 6 weeks

followed by a 2-week rest period (17 patients were continued without the 2-week break). Thalidomide was also given to 73 of the patients, and 7 patients received low-dose interferon alfa. The median duration of TMZ treatment was 113 days; 29% received > 24 weeks of therapy.

Upon retrospective analysis, lymphopenia was observed in 60% of patients (absolute lymphocyte count of < 800/uL) with a median of 101 days of treatment to lymphopenia. TMZ did not cause significant neutropenia or thrombocytopenia. Lymphopenia was not more common in patients treated concomitantly with thalidomide. In all patients analyzed for lymphocyte subsets, lymphopenia induced by TMZ affected the CD4+ compartment preferentially. One patient developed documented *Pneumocystis carinii* pneumonia, with another 2 patients meeting clinical criteria that were not biopsy-proven. In addition, one case of *Aspergillus pneumonia*, 4 cases of *Herpes simplex*, 4 cases of *Herpes zoster*, 11 cases of mucocutaneous candidiasis, and 1 case of Kaposi's sarcoma were observed. All of the patients who developed infections were lymphopenic except for 2 patients who developed *Herpes zoster* and 2 patients who developed mucocutaneous candidiasis.

COMMENT BY WILLIAM B. ERSHLER, MD

The treatment of melanoma remains frustrating. DTIC is the only FDA-approved chemotherapeutic agent for this indication, and combinations, including biotherapies, have not proven to offer any advantage in long-term survival. TMZ, when used in the 5-day/month schedule is comparable and offers the practical advantage of oral administration. The more intensive regimen used at Memorial is a reasonable approach to improving efficacy. Su and colleagues are to be credited for recognizing the treatment-associated immunodeficiency as indicated by the CD4+ lymphopenia and reporting the disproportionate occurrence of opportunistic infection.

As pointed out by Su et al, and in an accompanying editorial,[2] there are several important clinical implications of this report. First, if it turns out that the more intensive TMZ schedule offers improved outcomes in terms of tumor regressions and prolonged survival, then it would be prudent to consider *Pneumocystis carinii* pneumonia prophylaxis in treated patients and subject all treated patients to careful scrutiny for opportunistic infections. Secondly, evolving treatment strategies that involve immunomodulating approaches will need to take into consideration the deflating effect of TMZ on CD4 cell number and presumably function. For example, strategies that involve co-administration of interleukin-2 may be ineffective because of the countering effect of TMZ on the target cells of the immunoenhancing cytokine.

Finally, clinical investigators aware of the TMZ effect on CD4 T cells may explore the role of this drug as an immunosuppressant (eg, in the post-transplant setting) or in the treatment of tumors of CD4 lineage, such as in subsets of cutaneous T-cell lymphomas.

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Enthusiasm for Cancer Screening in the United States

ABSTRACT & COMMENTARY

Synopsis: *Most Americans believe that screening tests for cancer save lives and that it is irresponsible not to undergo recommended periodic screening. The presence of a large "market" for cancer screening may make Americans vulnerable to unproven and unnecessary testing.*

Source: Schwartz LM, et al. *JAMA*. 2004;291:71-78.

The aim of the present investigation was to document American's attitudes toward cancer screening using a telephone survey and a well-honed and validated inventory. The study was limited to women older than age 40 and men older than age 50 who were free of the diagnosis of cancer. Five hundred respondents were queried about 5 possible domains: general screening, colonoscopy or sigmoidoscopy, Pap smears and mammography in women, and prostate-specific antigen in men. The interviews ranged from 10 to 54 minutes.

Most adults (87%) believed that routine cancer screening was a good idea and that screening saved lives. Two-thirds would want to be tested even if nothing could be done if a cancer were discovered. Whereas 35% believed that they had had too few screening tests, only 2% felt that they had had too many. If told by a physician that they needed less frequent testing, most would overrule their physician and want to be tested. Indeed, 77 % of men would undergo PSA testing even if their physician would not advise it, and 58 % of women would want a Pap smear even if their physician

said it was unnecessary. Despite the "bad press" regarding the use of mammography, most women believe it is worthwhile. Most respondents felt that it was "irresponsible" to not undergo screening, even if the age of the individual to be screened were 80 years old. More than half of the respondents had had a false-positive screening test in the past, but 98% of those were glad they had the test and were planning to undergo additional testing. After being told that a total-body CT could "look inside your body" and give a very detailed picture of internal organs and that it was quick and painless, 86% volunteered to have one for free. When offered $1000 cash in exchange for the test, most still wanted the test.

COMMENT BY SARAH L. BERGA, MD

In a recent issue, I reviewed the pros and cons of optical vs conventional colonoscopy for screening for colon cancer. I had just seen a huge billboard advertising optical colonoscopy along the highway and it had garnered my interest in the use of this new technique. Apparently, I am not alone in being interested in new ways of being screened for cancer. The present article documents just how thoroughly indoctrinated most Americans are with regard to the necessity and value of cancer screening. Apparently, for the vast majority of us, physicians or not, more screening is clearly better, regardless of cost, discomfort, false positives, and emotional distress. This is a very important and timely topic for those of us practicing obstetrics and gynecology, because a prime reason our patients see us annually is to have their Pap smear and to make sure that they are up to date on well-care screening, especially mammography. Because many patients groan at least a bit when you remind them of the need for interval screening, I was surprised to find that these protests do not actually reflect what patients truly feel and think. Indeed, as noted above, even if the physician said that screening was unnecessary, most would still want to be screened.

Is screening necessary and if so, what type and how often? While physicians and public health experts debate the topic on the basis of cost, cost per saved life, risk, false negatives, and false positives, patients think, "more is better." Indeed, they may lose faith in a physician who does not screen often or thoroughly enough. If the results of this study ring true, then the prudent physician should be certain to create a checklist to review with patients regarding screening exams. The American College of Obstetricians and Gynecologists has created a helpful pamphlet that reviews what is needed by age categories for women. In the meantime, I expect that the hype about newer and more costly methods of screening for cancer will escalate. Those who make and/or perform these tests are well aware of the appetite and market that exists. Schwartz and colleagues conclude that these attitudes make Americans vulnerable to unproven and uninterpretable testing, such as screening for "cancer genes." Physicians have an opportunity and responsibility to provide a balanced viewpoint to counter aggressive marketing. ■

Dr. Berga is James Robert McCord Professor and Chair, Department of Gynecology and Obstetrics; Emory University School of Medicine, Atlanta, GA.

Myometrial Invasion and the Tumor-Free Distance from the Uterine Serosa in Endometrial Cancer?

ABSTRACT & COMMENTARY

Synopsis: *TFD as a single measurement carries significant prognostic importance in women with comprehensively staged endometrial cancer.*

Source: Lindauer J, et al. *Gynecol Oncol*. 2003;91(3):547-551.

Lindauer and colleagues set out to evaluate whether the tumor-free distance from the uterine serosa to the deepest invasive lesion was a better predictor of patient outcome from endometrial cancer than the traditional measure of myometrial invasion. To do this, they retrospectively evaluated all surgically staged endometrial adenocarcinoma patients between 1997 and 2000. Depth of myometrial invasion was defined as the distance in millimeters between the endometrial-myometrial junction and the deepest invasive lesion. Tumor-free distance was defined as the distance in millimeters between the uterine serosa and the deepest area of myometrial invasion. Depth of invasion and tumor-free distance were expressed as continuous variables in this report. To determine their predictive and prognostic significance, these 2 variables were compared with traditional surgicopathologic factors and against outcomes of recurrence and survival. A total of 153 patients met study criteria. The most common stage was IB, and 23 patients had positive nodes. The median depth of invasion was 0.5 cm and the median tumor-free distance was 1.4 cm. At a median follow-up of 29 months, 10 patients recurred. By univariate analysis, both invasion

parameters were significant predictors of traditional surgicopathologic variables.

However, only tumor-free distance was predictive of recurrence. In addition, while both tumor-free distance and depth of invasion were significant predictors of survival, only tumor-free distance was correlative with surgicopathologic variables and predictive of recurrence and survival in the multivariate model. Depth of invasion became predictive of recurrence when myometrial thickness was included in the model. A tumor-free distance of 1 cm maximized the balance of sensitivity and specificity in predicting recurrence. Lindauer et al concluded that tumor-free distance as a single continuous measurement carries significant prognostic importance in women with comprehensively staged endometrial cancer.

COMMENT BY ROBERT L. COLEMAN, MD

Epithelial malignancy of the uterine corpus remains the most common gynecological malignancy diagnosed in the United States. Characterized by frequent early stage at diagnosis, endometrial cancer is often considered a "curable" lesion. However, more than 20% of clinical stage I cases will have evidence of extrauterine disease, and up to 15% will recur at 5 years.[1,2] Exhaustive evaluation of important clinicopathological risk factors relating to these clinical outcomes, along with survival, led FIGO to modify the staging schema in 1988, incorporating findings at surgery generated from formal exploration. Currently, surgical staging is recommended for all patients with the diagnosis.[3] Nonetheless, it is a rare event for noninvasive lesions to be associated with metastatic disease, prompting some to use a measure of grade and gross myometrial invasion to triage those who should undergo the more extensive surgical staging procedure.[4,5] However, unreliable and inconsistent correlation of intraoperative findings to final postoperative pathology hallmarks the challenge of making an accurate assessment of myometrial invasion and thus, leading potentially to improper staging—raising yet another challenge in determining accurate postoperative therapy.

Lindauer et al study another methodology for quantifying myometrial invasion by looking at, essentially, the complement of the standardized practice. This measure of tumor-free distance from the serosa to the deepest element of invasion is easier to measure and, through multivariate analysis, was better associated with parameters determining survival. A tumor-free distance of 1 cm was associated with the best probability testing characteristics for recurrence. Although not an *a priori* goal, Lindauer et al did have 2 pathologists evaluate a limited number of specimens for this parameter. The reproducibility was quite high, being identical in 4 of 5 cases tested.

It is of note that traditionally measured depth of myometrial invasion became an important independent variable when myometrial thickness was also considered. It is from this "denominator" that percent of myometrial invasion is calculated and reported. In the current study, depth of myometrial invasion was considered as a continuous variable without relation to the uterine wall. In this respect, it is not difficult to see why the variable fell out on multivariate testing. For instance, a 0.75 cm invasive lesion in a 3.0 cm uterine wall (25% invasion) would be expected to behave differently (and staged differently) than the same 0.75 cm lesion in a wall 1.0 cm thick (75% invasion). Calculating a percent invasion "normalizes" to some extent the invasion characteristic and as such brings the measure more in line with what tumor-free distance is essentially measuring. My suspicion is that the 2 variables would explain similar amounts of variance on regression testing if compared. Parenthetically, similar strategies for assessing biological behavior have been reported in carcinoma of the cervix, with short tumor-free distances frequently associated with nodal metastases. Whichever methodology is ultimately used, the growing trend in the surgical evaluation of endometrial cancer is to perform complete surgical staging wherein an accurate picture of the disease state can be constructed to effectively counsel and treat patients with this malignancy. ■

Dr. Coleman is an oncologist in the Dept. of Gynecologic Oncology, University of Texas Southwestern Medical Center, Dallas, Tex.

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CME Questions

9. The appearance of myelosuppression (neutropenia, thrombocytopenia, or both) in chronic-phase CML patients treated with imatinib mesylate (Gleevec®) was shown in the series of 143 patients treated at M.D. Anderson to influence all but which of the following?

a. amount of dose of imatinib delivered
b. major cytogenetic response rate
c. complete cytogenetic response rate
d. 5-year survival

10. Which of the following statements about lymphoma management in the elderly is supported by the findings presented in the series reported from Korea?

a. Older patients with diffuse lymphoma, in general, have remission rates comparable to younger patients.
b. Older patients with diffuse lymphoma who are able to maintain a treatment schedule with a doxorubicin intensity of > 10 mg/m^2/wk had remission rates comparable to younger patients.
c. Older patients with diffuse lymphoma who are able to maintain a treatment schedule with a doxorubicin intensity of > 10 mg/m^2/wk had remission rates that remained significantly less favorable when compared to younger patients.
d. Older patients with diffuse lymphoma who were treated with primary G-CSF had fewer episodes of febrile neutropenia and better overall survival than similar patients treated with G-CSF only after febrile neutropenia occurred.

11. Daily temozolomide treatment of melanoma patients for extended periods as opposed to the more commonly used 5 day/month regimen was shown to:

a. enhance remission rates and overall survival.
b. produce significant levels of neutropenia and associated bacterial infections.
c. produce significant lymphopenia and associated opportunistic infections.
d. All of the above

Answers: 9 (d); 10 (b); 11 (c)

In Future Issues:

Complementary and Alternative Medication Useage by Cancer Patients

PHARMACOLOGY WATCH

Sinus and Allergy Health Partnership Releases New Guidelines for Treatment of Bacterial Rhinosinusitis

New guidelines for the treatment of bacterial rhinosinusitis were published in the January supplement of *Otolaryngology- Head and Neck Surgery* by the Sinus and Allergy Health Partnership. The goal of the guidelines is to reduce the use of antibiotics for viral infections and to use the most appropriate antibiotic for bacterial infections. The guidelines recommend antibiotics if patients are getting worse after 5-7 days or if they are not better after 10-14 days. Patients with mild disease should be treated with cefpodoxime (Vantin), cefuroxime (Ceftin), amoxicillin, amoxicillin/clavulanate (Augmentin), or cefdinir (Omnicef). Patients with moderate disease or those with recent antibiotic exposure should receive amoxicillin/clavulanate, ceftriaxone, or one of the respiratory fluoroquinolones including gatifloxacin (Tequin), moxifloxacin (Avelox), or levofloxacin (Levaquin). The respiratory quinolones do not include ciprofloxacin. This is a follow-up to the group's first guidelines, which were published in 2000 (*Otolaryngol Head Neck Surg*. Supplement. 2004;130:1).

Steroids Not Linked to Risk of Fractures

Long-term use of inhaled steroids for the treatment of respiratory diseases or nasal steroids for the treatment of allergic rhinitis are not associated with an increased risk of fractures if they are used in normal doses, according to a study from Canada. Researchers conducted a case-control study of all elderly Québec residents who were dispensed respiratory medications and could be followed for at least 4 years from 1988 to 2001. The rate of hip or upper extremity fractures was not increased in those patients who used daily inhaled corticosteroids (RR, 0.97). The rate of upper extremity fractures increased by 12% with every 1000 µg increase in the daily inhaled corticosteroid, but the rate of hip fractures did not increase. The rate of hip fractures was only elevated with very high doses (more than 2000 µg per day) of inhaled corticosteroid. Nasal steroids did not increase the risk at any dose. The authors conclude that long-term use of inhaled and nasal corticosteroids at usual recommended doses is not associated with the risk of fracture (*Am J Resp Crit Care Med*. 2004;169:83-88).

ADT Puts Men at Risk for Osteoporosis

Men treated for prostate cancer with androgen deprivation therapy (ADT) are at risk for osteoporosis and fractures, according to a new study. One year of ADT resulted in 2-8% bone loss in the lumbar spine and 1.8-6.5% bone loss

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5413. E-mail: christie.petrone@ thomson.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

in the femoral neck. The study was a meta-analysis of 9 studies that included a total of 208 patients. The authors suggest that men starting ADT should be considered for bone mineral density measurement, and men at high risk should be offered a bisphosphonate (published online January 19, 2004. *Cancer*).

Study Shows Valsartan May Improve Sexual Function in Postmenopausal Women

A new study suggests that valsartan may improve sexual function in hypertensive postmenopausal women. Researchers randomized 120 postmenopausal women aged 51-55 with mild-to-moderate hypertension to valsartan 80 mg daily or atenolol 50 mg daily for 16 weeks. Doses were doubled if diastolic blood pressures remained above 90 mm Hg. The end point was a questionnaire that self-evaluated various aspects of sexual desire, orgasmic response, and coital activity. The drugs lowered blood pressure equally effectively. Women in the valsartan group noted significantly improved sexual desire (38% increase, $P < .01$), changes in behavior (45% increase, $P < .001$), and sexual fantasies (51% increase, $P < .001$). In the atenolol group, scores for sexual desire and sexual fantasies significantly worsened (18% decrease, $P < .01$, and 23% decrease, $P < .001$, respectively). The authors conclude that in the study group, hypertensive postmenopausal women in their 50s, valsartan improved some aspects of sexual function, whereas atenolol worsened it. They further speculate the drugs may have differential effects on serum hormone levels, specifically testosterone (*Am J Hyperten*. 2004;14:77-81).

New Direct-to-Consumer Pharma Advertising Rules Considered

Anyone who watched the Super Bowl can verify that direct-to-consumer advertising of prescription pharmaceuticals is big business. Now the FDA is considering tighter restrictions on the content of these ads, requiring pharmaceutical companies to highlight key risks associated with the drugs rather than listing the large number of potential side effects in small print. The guidelines encourage companies to use less cluttered formats for print ads, perhaps even using bullet points to set the import risks apart. Print ads currently contain an extensive list of side effects similar to the package insert, often in a similarly small font, frequently on a separate page from the main advertisement. The FDA is also considering changing the criteria for "reminder" ads that simply name the drug without giving the indication for its use. Currently, these ads do not require information on adverse effects and often run close to disease awareness campaigns also paid for by the drug company. These new FDA restrictions have not been finalized and are sure to be opposed by Pharma.

FDA Actions

Boehringer Ingelheim Pharmaceuticals has received FDA approval to market tiotropium bromide inhalation powder (Spiriva) for the treatment of COPD. Tiotropium, a once-daily anticholinergic agent, is indicated for the long-term maintenance treatment of bronchospasm associated with COPD.

Modafinil (Provigil) has been approved for improving wakefulness in patients with excessive sleepiness due to obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. The drug is currently approved for improving wakefulness in patients with narcolepsy.

The FDA has approved a 3-day course of azithromycin (Zithromax) for the treatment of acute bacterial sinusitis. The drug, which is dosed at 500 mg once a day, is the only 3-day regimen approved for this indication. Azithromycin is currently approved for the treatment of community-acquired respiratory infections and skin infections, as well as otitis media.

Olanzapine (Zyprexa) has been approved for maintenance treatment of bipolar disorder. The drug appears to be effective in delaying relapse into either mania or depression in bipolar patients. Olanzapine was approved in 2000 for the short-term treatment of acute mixed or manic episodes associated with bipolar disorder.

The FDA has also approved a combination of olanzapine and fluoxetine (Prozac) for the treatment of bipolar depression. The combination drug will be marketed under the trade name Symbyax. Quetiapine fumarate (Seroquel) was also recently approved for monotherapy and adjunct therapy with lithium and divalproex, for the short-term treatment of acute manic episodes associate with bipolar I disorder. ■